CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH
SUMMARY OF TOXICOLOGY DATA

DESMEDIPHAM

Chemical Code # 001748; Tolerance # 00353; SB 950 # 050

July 20, 2000

I. DATA GAP STATUS

Combined, Rat (Chronic/onco):	No data gap, no adverse effect.
Chronic Toxicity, Dog:	No data gap, no adverse effect.
Oncogenicity, Mouse:	No data gap, no adverse effect.
Reproduction, Rat:	No data gap, no adverse effect.
Teratology, Rat:	No data gap, possible adverse effect.
Teratology, Rabbit:	No data gap, no adverse effect.
Gene Mutation:	No data gap, possible adverse effect.
Chromosomal Aberration:	No data gap, no adverse effect.
DNA Damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.
Record numbers #069352 – 58; 017645 & 017646; 034521 - 26, 045513 and 962782 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T000720
Toxicology Summary prepared by Kishiyama & Silva, 7/20/00.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

** 051 069357 "T56-Desmedipham: 2 Year Chronic Toxicity/Oncogenicity Study with Desmedipham Technical in Rats - Dietary Administration," (Suter, P., Horst, K., Luetkemeier, H., Vogel, W., Pappritz, G., Terrier, CH., Sachsse, K.; Research Consulting Co., Ag, CH4452, Itingen/Switzerland, Laboratory Project ID No. PF 83.810, 9/25/86). Desmedipham technical (purity = 98.1%) was fed in diet to Wistar KFM-Han SPF rats (70/sex/dose; 50 or 20/sex/dose for onco & chronic groups, respectively) at 0, 60, 300, or 1500 ppm. Chronic NOEL = 3.2 mg/kg/day (Body weights were reduced in males at $\geq$ 300 ppm and in females at 1500 ppm. Hematology indicated toxic hemolytic anemia with a compensatory erythrogenic response, according to the report. Erythrocyte count (RBC), HB and HCT were decreased in males at $\geq$ 300 ppm and in females at 1500 ppm. MCHC was decreased in both sexes at 1500 ppm. MCV, MCH, RETIC., Heinz-body and MET-HB were increased in both sexes at > 300 ppm. Total bilirubin increased in both sexes at 1500 ppm. Females had lower T4 level at $\geq$ 300 ppm. Males had decreased T4 at 1500 ppm. Females at $\geq$ 300 ppm had lower T3. Spleen weights were increased in both sexes at 1500 ppm. Thyroid Gland had an increased incidence in hyperplasia in males ($\geq$ 300 ppm) and in females (1500 ppm). Spleen had erythropoiesis and hemosiderosis increase in both sexes at 1500 ppm.) No oncogenic effects were reported. No adverse effect. ACCEPTABLE. (Kishiyama & Silva, 5/24/00).

CHRONIC TOXICITY, DOG

Subchronic Study:

** 047 069353 "Technical Desmedipham: 90-Day Dietary Study in the Dog," (Hounsell, I.A. & Martin, P.L.; FBC Limited, Chesterfield Park Research Station, Safford Walden, Essex CB10 1XL, UK; Study #: TOX/85055; Report #: TOX/86/198-11; 9/3/86). Desmedipham technical (purity = 97.8%) was fed in diet to Beagle dogs (4/sex/dose) at 0, 1, 5 or 150 ppm for 90 days. NOEL = 5 ppm; 0.18 mg/kg (There was a significant increase in methaemoglobin at 150 ppm in both sexes. Both sexes had effects in the blood at 150 ppm. There was an increase in hemorrhagic cystitis in female urinary bladder and mononuclear cell infiltrations in the parotid salivary gland at 150 ppm.) Acceptable. No adverse effect. (Kishiyama & Silva, 6/7/00).

Chronic Study:

** **048 069354** "12-Month Oral Toxicity (Feeding) Study with Desmedipham Technical in Beagle Dogs" (Bathe, R.; Research Consulting Company, AG, CH4452, Itingen/Switzerland, Project #: 011913; 1/14/85). Desmedipham technical (purity = 97.8%) was fed in diet to Beagle dogs (6/sex/dose) at 0, 300, 1500 and 7500/5000 ppm (corrected daily dosage: 0, 9.8, 53, 241, then 171 mg/kg) for 12 months. At 13 weeks, 2/sex/dose were terminated. The high dose was initially 7500 ppm (1st 28 days) but was reduced to 5000 ppm. Possible adverse effect: **Desmedipham is reported to cause toxic hemolytic anemia.**

NOEL = 300 ppm/day (Food consumption was decreased at 7500 ppm. At 5000 ppm, food consumption remained less than controls for females. Body weight was reduced in both sexes at the high dose. At 1500 ppm, female body weights were decreased by week 18. Bodyweight gains were also reduced in females during weeks 1 to 18 at 1500 ppm. Treatment related changes were decreased urea (5000 ppm-M), T3 (all doses) and T4 (≥ 1500 ppm-F), increased total bilirubin (1500 ppm), total cholesterol (5000 ppm), lactate dehydrogenase (5000 ppm-M) and alkaline phosphatase (5000 ppm-F). Plasma protein fractions changed (decreased albumin & increased ?-globulin) at 5000 ppm. Spleen (males), liver and thyroid weights were increased in both sexes at ≥ 1500 ppm. Bone marrow, spleen and liver erythropoiesis were increased in both sexes (primarily female) at ≥ 1500 ppm. Liver iron deposition and thyroid follicular hyperplasia were increased (M-500 ppm & F- ≥ 1500 ppm). ACCEPTABLE. (Kishiyama & Silva, 7/7/00

**** 048, 062 069354, 115499** Original Report: "12-Month Oral Toxicity (Feeding) Study with Desmedipham Technical in Beagle Dogs," (Bathe, R.; Research Consulting Co., AG, CH4452, Itingen/Switzerland, Project No. 011913; 1/14/85). Supplement: "Determination of the No-Effect Level for Methemoglobin Production Following Desmedipham Technical Administration in the dog (Oral/Feeding Route)," (Allen, T.R., Corney, S.J., Frei, Th., Biedermann, K., Luetkemeier, H., Vogel, O., Pappritz, G.; RCC Research and Consulting Company, AG; RCC Umweltchemie AG; PATCO Experimental Pathology Consulting AG, Itingen/Switzerland; RCC Project #: 250288; Schering Study #: TB 89 055; 12/7/89). Desmedipham technical (purity = 97.6%) was fed in diet to beagle dogs (2/sex/group) at 0, 150/200/500 ppm for 21-80 days (3 - 12 weeks) and 75/300/0/1500 ppm for 80 days (with periodic change in dose). The purpose of the study was to determine the NOEL for methemoglobin production. NOEL = 300 ppm (Methemoglobinemia increased in both sexes when desmedipham was administered in the feed at 1500 ppm (after 5 days) and in females at 500 ppm (after 2 days).) These data are supplemental. (Kishiyama & Silva, 6/9/00).

ONCOGENICITY, MOUSE

Subchronic Study:

061 115498 "A 28-Day Oral Toxicity (Feeding) Study with Desmedipham Technical in Mice," (Suter, P., Horst, K., Lind, H., Luetkemeier, H., Terrier, Ch., Chevalier, J.; RCC Research & Consulting Company, AG, Laboratory Project I.D. RCC 020946; Nor-Am Report #: T38;11/5/84). Desmedipham technical (97.8% pure) was fed in diet to SPF mice (10/sex/dose) at 0, 100, 400 or 1600 ppm for 28 days (M: 22, 91 & 416 mg/kg bwt/day; F: 26, 108 & 519 mg/kg bwt/day. No clinical effects or reduced bodyweight and/or food consumption was observed. NOEL < 100 ppm (Dose-dependent increased extramedullary hemopoiesis (erythropoiesis) occurred among all treated groups in both sexes. Erythropoiesis increased in bone marrow of males at 1600 ppm. Heinz body and methemoglobin were increased in both sexes at ≥ 400 ppm (toxic hemolytic anemia). Males had decreased HB and MCHC (≥ 400 ppm) and RBC (1600 ppm). Spleen, (M & F, 1600 ppm), heart and kidney weights increased (F,1600 ppm).) Possible adverse effect indicated (Hemolytic effects were observed at all doses.) (Kishiyama & Silva, 6/7/00).

Oncogenicity Study:

** 050 069355 "104-Week Oncogenicity Study with Desmedipham Technical in Mice - Dietary Administration," (Suter, P., Horst, K., Vogel, W., Luetkemeier, H., Westen, H., Terrier, Ch., Sachsse, K.; Research Consulting Co., AG, CH4452, Itingen, Switzerland, Project 020957, 9/15/86). Desmedipham technical (purity = 97.8%) was fed in diet to NMRI mice (10 & 50/sex/dose for 52 weeks & 104 weeks) at 0, 30, 150, or 750 ppm/day (M: 4.2, 22 & 109 mg/kg; F: 5.8, 31 & 145 mg/kg). NOEL = 21.68 mg/kg/day (M); 30.75 mg/kg/day (F) (Bodyweight for males was reduced 9.7 - 20.0% weeks 1 - 51 (Interim group) and 5.6 - 9.3% (Onco group) weeks 25 - 45. HB and HCT were decreased in females at 750 ppm, week 52. Heinz bodies were increased in both sexes at weeks 52 and 104. MET-HB was increased in both sexes at Week 52. Males (52 weeks) had increased relative kidney weights at 750 ppm. Females had increased absolute and relative spleen weights at 52 weeks.) No oncogenicity was observed. ACCEPTABLE. No adverse effects. (Kishiyama & Silva, 5/23/00).

061 115497 "NOR-AM Response to EPA Review of Mouse Oncogenicity Study T55, 9/30/91" This attachment contains a response by NOR-AM to EPA's review of the mouse oncogenicity study. M. Silva, 7/14/00.

REPRODUCTION, RAT

** 049 069356, "Multiple Generation Reproduction Study with Desmedipham Technical in Rats," (Becker, H., Frei, D., Vogel, W., Pappritz, G., Terrier, Ch.; Research Consulting Co., AG, CH4452, Itingen/Switzerland, RCC project #: 015276; Schering Project #: PF-82.810; 7/1/86). Desmedipham technical (purity = 97.8%) was fed in diet to Wistar KFM-Han rats (30/sex/dose—F0; 26/sex/dose—F1) at 0, 50, 250 and 1250 ppm during pre-mating (80 days F0; 100 days F1), during mating, gestation and lactation (2 litters/generation). Parental NOEL = 50 ppm (F1 parents of both sexes had decreased bodyweights and food consumption at 1250 ppm. F0 parents of both sexes had decreased bodyweights at 1250 ppm. F0 males at 1250 ppm had increased spleen weights and decreased kidney weights. F0 females at 1250 ppm had increased spleen weights and decreased thymic and uterine weights. F1 females at $\geq$ 250 ppm had increased spleen weights. F1 (both sexes) at 1250 ppm had increased liver hemosiderosis and liver multifocal extramedullary hemopoiesis. F1 males had increased spleen hemosiderosis and hemopoiesis at $\geq$ 250 ppm (F1 females at 1250 ppm). F1 (both sexes) had increased thyroid gland follicular hyperplasia and males had increased bone marrow erythroid hyperplasia at 1250 ppm.) Reproductive NOEL = 1250 ppm (There were no reproductive effects observed at any dose.) Pup NOEL = 250 ppm (F1a & b pups had lower body weight by the end of lactation at 1250 ppm.) No adverse reproductive effect. (Kishiyama & Silva, 7/5/00).

047 069352 "Preliminary Study to the Multiple Generation Reproduction Study with Desmedipham Technical in Rats," (Becker, H., Frei, D., Lind, H., Chevalier, J., Terrier, Ch.; Research Consulting Co., Ag, CH4452, Itingen/Switzerland, Project No. RCC 015221, 11/15/84). Desmedipham technical (purity = 97.8%) was fed in diet to Wistar KFM-Han rats (10/sex/dose) at 0, 300, 1500, or 7500 ppm for 3 weeks premating and throughout mating, gestation and lactation. High dose was excluded from evaluation (40% of group failed to mate; larger spleen weight). Parental NOEL = 300 ppm (Food consumption was lower during the desmedipham treatment, primarily at $\geq$ 1500 ppm. Body weight was decreased in both sexes at 7500 ppm. High dose males had enlarged kidneys. There was increased spleen weight in both sexes at

1500 ppm.) Reproductive NOEL = 1500 ppm (It was not possible to evaluate reproductive effects at 7500 ppm, due to low fertility (only 1/10 gave birth).) Pup NOEL = 300 ppm (There was decreased bodyweight gain at 1500 ppm.) (Kishiyama & Silva, 5/25/00).

TERATOLOGY, RAT

**** 036 045513**, "Embryotoxicity (including teratogenicity) Studies with Desmedipham Technical in the Rat (Studies 1 & 2)", (Study 1: Becker, H., Frei, D., Vogel, W., Terrier, Ch., Sachsse, K., Schafroth, P., Luetkemeier, H.; Study 2: Becker, H., Schafroth, P., Vogel, W., Luetkemeier, H., Terrier, Ch., Sachsse, K.; Research Consulting Co. AG, Study (Project no. 024996 & 043053), 6/6/85 and Study 2 (project 043053), 11/21/85). Study 1: Desmedipham technical (97.8% pure) was administered by gavage to mated Wistar KFM-Han rats (25/dose) at 0 (2% CMC in distilled water), 10, 100 or 1000 mg/kg (limit test) on days 6-15 post-coitum (pc). **Maternal NOEL =** 100 mg/kg (Body weights and food consumption decreased at 1000 mg/kg.) **Developmental NOEL =** 10 mg/kg (A dose-related increase in anomalies occurred, primarily at 1000 mg/kg.) **Possible adverse effect: mandibular malformations at = 100 mg/kg.)** Study 2: The same protocol as Study 1, with doses of 0, 10, 100 and 500 mg/kg (35 rats/dose). **Maternal NOEL =** 100 mg/kg/day (Body weight gain and food consumption were decreased at 500 mg/kg. At 500 mg/kg, there was a significant increase in Heinz-bodies (toxic hemolytic anemia). **Hematological Maternal NOEL** = 10 mg/kg (Methemoglobin increased at $\geq$ 100 mg/kg (not a FIFRA requirement for developmental studies). **Developmental NOEL =** 100 mg/kg (**Possible Adverse Effect: 3-4% (litter) incidence of mandibular micrognathia.** Each study is acceptable alone. (Kishiyama & Silva, 6/1/00).

014 962782, "Teratogenic Study with EP 475 (SN38107 Technical) in albino Rats" (Industrial Bio-Test Laboratories Inc., IBT 8585, February 1972). UNACCEPTABLE. INVALID STUDY. (J. Remsen, 3/20/85).

063 115500 This volume contained an amended Table 2 from "Embryotoxicity (including teratogenicity) Studies with Desmedipham Technical in the Rat (Studies 1 & 2)", (original report). Table 2 held data from an analysis of desmedipham technical in carboxymethylcellulose suspensions. The amended table contained an indication (top, middle, bottom) of where samples were taken from in the mixing container. There were no new data. M. Silva, 7/13/00.

TERATOLOGY, RABBIT

** 035, 063 & 064 034521, 115501, 115503, 115505 – 06 "T23 (including addendum) DESMEDIPHAM TECHNICAL: Embryotoxicity (including teratogenicity) Study With Desmedipham Technical," (Becker, H.; Research & Consulting Company AG, Iringen, Switzerland; Laboratory Project ID#: 014613; 6/6/84). Desmedipham technical (97.8% pure) was administered by gavage to mated hybrid Chinchilla rabbits (16/dose) at 0 (vehicle = 2% carboxymethylcellulose), 50, 150 and 450 mg/kg/day during days 6 – 27 *post coitum* (pc). Maternal NOEL = 150 mg/kg (At 450 mg/kg, dams had decreased food

consumption and bodyweights. Postimplantation loss and abortions were increased at 450 mg/kg.) Developmental NOEL = 150 mg/kg (Fetal bodyweights were decreased at 450 mg/kg.) This study was previously reviewed as unacceptable but upgradeable (Parker, 10/24/85). Upon submission of the requested information, the study has been upgraded to acceptable for filling the rabbit teratology data gap, with no adverse effect. M. Silva, 7/14/00.

029 017646, 1. An IBT Replacement Study. 2. Partial duplicate of 035 034521. 3. Submitted earlier than 034521. "Embryotoxicity (including teratogenicity) Study with Desmedipham Technical", (Research & Consulting Co., Ltd., Project 014613, May 1983). Desmedipham technical, purity 97.8%, administered by oral gavage at concentrations of 0 (2% CMC in distilled water, 50, 150, or 450 mg/kg/day to 16 mated female chinchilla Hybrid rabbits/dose from day 6 though 27 of pregnancy. The report states no teratogenic effects were found. UNACCEPTABLE. Insufficient information (pages missing). (J. Remsen, 3/20/85).

029 017645. Range-finding study for 034521. "Dose-Finding Embryotoxicity (including teratogenicity) Study with Desmedipham Technical", (Research & Consulting Co., Ltd., Project 013274, March 1983). (J. Remsen, 3/20/85).

GENE MUTATION

** **035 034522**, "Technical Desmedipham: Mouse Lymphoma Mutation Assay", (Inveresk Research International, Scotland, 2/18/85). Desmedipham, technical, purity of 98%, at concentrations of 0, 6.3, 12.5, 25, 50, 100, and 200 µg/ml in the 1st assay and at 20, 40, 60, 80. 100, and 120 µg/ml in a 2nd assay for 4 hours to mouse lymphoma cells with and without metabolic activation (rat liver). **Adverse effect: Increased mutation frequency** at the higher concentrations (with and without rat liver activation in both assays. ACCEPTABLE. (V. Van Way, 10/20/85; J. Remsen 10/23/85).

** 064 115509 "AT79 Desmedipham: *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay with Desmedipham," (Poth, A.; CCr Cytotest Cell Research GmbH & Co KG, Robdorf, FRG; Laboratory Study & Report #'s: CCR 169108, TB 89 057; 6/14/90). Desmedipham technical (97.6% pure) was used at 0, 10, 33.3, 100, 333.3, 666.6, 1000 and 5000 µg/plate (+/- S9 mix) on *Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA 1537 and *Escherichia coli* WP2 strain to evaluate mutagenic potential. There was no significant increase in mutagenicity with either *S. typhimurium* or *E. coli* after desmedipham treatment. ACCEPTABLE. (Kishiyama & Silva, 6/9/00).

CHROMOSOME EFFECTS

** 035 034523, "Mouse Micronucleus Assay with Desmedipham Technical", (Research and Consulting Co., Itingen, Switzerland, 5/4/85). Technical Desmedipham, purity 98.3%, administered by gavage (single dose) at a concentration of 0 (2% carboxymethylcellulose) and 5000 mg/kg at intervals of 24, 48 and 72 hours to 5 "NMR1" KFM (outbred SPF quality) mice/sex. NOEL = >5000 mg/kg. No evidence of increased micronuclei or altered PCE/NCE. ACCEPTABLE. (V. Van Way 10/21/85; J. Remsen, 10/24/85).

** 035 034536, "Technical Desmedipham: Metaphase Chromosome Analysis of Human Lymphocytes cultured In Vitro", (Huntingdon Research Centre, England, 1/14/85). Desmedipham, technical, 98.0 purity, exposure concentrations of 0 (ethanol, DMSO, and Distilled water controls), 10, 50, and 100 µg/ml to human lymphocytes for 2 hours with and 22 hours without metabolic activation. No increase in aberrations with or without rat liver activation. ACCEPTABLE. (V. Van Way, 10/21/85; J. Remsen, 10/24/85).

DNA DAMAGE

** 035 069361 "T106-Phenmedipham: Mutagenicity Test on Phenmedipham Technical in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay," (Cifone. M.A.; Hazleton Laboratories America, Inc.; HLA Study #: 9947-0-447; Schering Project #: TB 87034;12/11/87). Phenmedipham technical (purity = 98.3%) was used on primary rat hepatocytes at 0 (DMSO), 2.5, 5.0, 10.0, 25.0, 37.5 or 50.0 µg/ml to detect DNA damage (2 cultures/dose for cytotoxicity & 3/dose for UDS). Phenmedipham did not induce detectable DNA damage/repair in the test system. There was no treatment-related increase in DNA unscheduled synthesis (UDS) at any dose. Positive controls functioned as expected. ACCEPTABLE with minor deficiencies. No adverse effect. (Kishiyama & Silva, 3/7/00).

NEUROTOXICITY

Not required at this time.